

**Amendments to the Claims:**

This listing of claims will replace all prior versions, and listings of claims in the application:

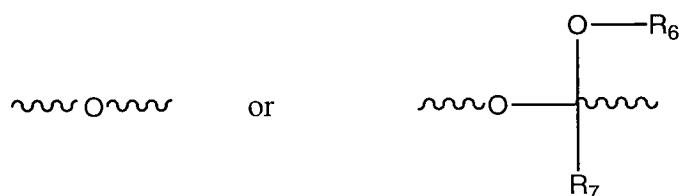
**Listing of Claims:**

1. (Withdrawn) A protected anti-neoplastic agent of the formula Hyp-L-N or Hyp-N, wherein

Hyp is a hypoxic activator;

N is an anti-neoplastic agent; and

L is a linking group of the formula  $\sim\sim\sim X - Y \sim\sim\sim$ , where X is selected from



where  $R_6$  is unsubstituted alkyl or alkyl substituted with one or more heteroatom containing groups;

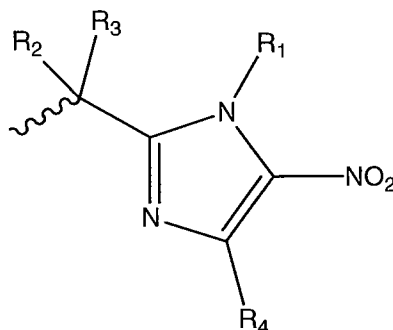
$R_7$  is hydrogen, unsubstituted alkyl or alkyl substituted with one or more heteroatom containing groups; and

Y is a spacer group selected from a substituted or unsubstituted  $-(CH_2)_n-$  chain with  $n=1-4$ ; a substituted or unsubstituted  $-(CH_2)_n-$  chain with  $n=1-4$  in which one of the carbon backbone chain atoms is substituted by a heteroatom containing group; and a delayed release group comprising an aromatic group.

2. (Withdrawn) The protected anti-neoplastic agent of claim 1, wherein the hypoxic activator is selected from the group consisting of electron deficient nitrobenzene moieties, electron deficient nitrobenzoic acid amide moieties, nitroazole moieties, nitroimidazole moieties, nitrothiophene moieties, nitrothiazole moieties, nitrooxazole moieties, nitrofuran moieties, and nitropyrrole moieties.

3. (Withdrawn) The protected anti-neoplastic agent of claim 2, wherein the hypoxic activator is a substituted or unsubstituted nitroimidazole moiety.

4. (Withdrawn) The protected anti-neoplastic agent of claim 3, wherein the hypoxic activator is a moiety of the formula



wherein

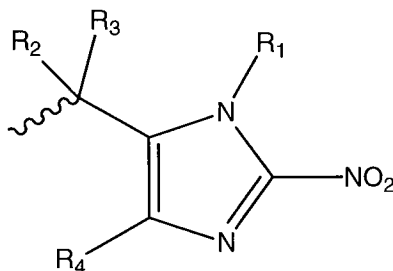
R<sub>2</sub> is hydrogen;

R<sub>3</sub> is hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sub>1</sub> is an electron withdrawing group, an unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkyl substituted with one or more heteroatom-containing groups, unsubstituted C<sub>1</sub>-C<sub>6</sub> alkoxy, or C<sub>1</sub>-C<sub>6</sub> alkoxy substituted with one or more heteroatom-containing groups; and

R<sub>4</sub> is an electron withdrawing group, -H, unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkyl substituted with one or more heteroatom-containing groups, unsubstituted C<sub>1</sub>-C<sub>6</sub> alkoxy, or C<sub>1</sub>-C<sub>6</sub> alkoxy substituted with one or more heteroatom-containing groups.

5. (Withdrawn) The protected anti-neoplastic agent of claim 3, wherein the hypoxic activator is a moiety of the formula



wherein

R<sub>2</sub> is hydrogen;

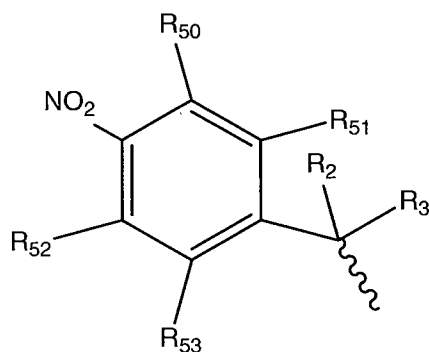
R<sub>3</sub> is hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sub>1</sub> is unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkyl substituted with one or more heteroatom-containing groups, unsubstituted C<sub>1</sub>-C<sub>6</sub> alkoxy, or C<sub>1</sub>-C<sub>6</sub> alkoxy substituted with one or more heteroatom-containing groups; and

R<sub>4</sub> is -H, unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkyl substituted with one or more heteroatom-containing groups, unsubstituted C<sub>1</sub>-C<sub>6</sub> alkoxy, or C<sub>1</sub>-C<sub>6</sub> alkoxy substituted with one or more heteroatom-containing groups.

6-16. (Canceled)

17. (Withdrawn) The protected anti-neoplastic agent of claim 2, wherein the hypoxic activator is a nitrobenzene of formula



where

R<sub>2</sub> is hydrogen;

R<sub>3</sub> is -H, C<sub>1</sub>-C<sub>6</sub> alkyl; and

R<sub>50</sub>, R<sub>51</sub>, R<sub>52</sub>, and R<sub>53</sub> are independently selected from an electron withdrawing group, H, C<sub>1-6</sub> alkyl or C<sub>1-6</sub> alkoxy; where the alkyl and alkoxy are optionally independently substituted with one or more groups selected from ether (-OR<sup>20</sup>), amino (-NH<sub>2</sub>), mono-substituted amino (-NR<sup>20</sup>H), di-substituted amino (-NR<sup>21</sup>R<sup>22</sup>), cyclic C<sub>1-5</sub> alkylamino, imidazolyl,

C<sub>1-6</sub> alkylpiperazinyl, morpholino, thiol (-SH), thioether -(SR<sup>20</sup>), tetrazole, carboxylic acid (-COOH), ester (-COOR<sup>20</sup>), amide (-CONH<sub>2</sub>), mono-substituted amide (-CONHR<sup>20</sup>), disubstituted amide (-CONR<sup>21</sup>R<sup>22</sup>), N-connected amide (-NH<sub>2</sub>-C(=O)-R<sup>20</sup>), mono-substituted N-connected amide (-NHR<sup>21</sup>-C(=O)-R<sup>20</sup>), disubstituted N-connected amide (-NR<sup>21</sup>R<sup>22</sup>-S(=O)<sub>2</sub>-R<sup>20</sup>), N-connected sulfonamide (-NH<sub>2</sub>-S(=O)<sub>2</sub>-R<sup>20</sup>), mono-substituted N-connected sulfonamide (-NHR<sup>21</sup>-S(=O)<sub>2</sub>-R<sup>20</sup>), disubstituted N-connected sulfonamide (-NR<sup>21</sup>R<sup>22</sup>-S(=O)<sub>2</sub>-R<sup>20</sup>), sulphonyl (-S(=O)<sub>2</sub>OH), sulphonate (S(=O)<sub>2</sub>OR<sup>20</sup>), sulphonyl (S(=O)<sub>2</sub>R<sup>20</sup>), sulphoxy (S(=O)OH), sulphinate (S(=O)OR<sup>20</sup>), sulphinyl (S(=O)R<sup>20</sup>), phosphonooxy (OP(=O)(OH)<sub>2</sub>), phosphate (OP(=O)(OR<sup>20</sup>)<sub>2</sub>), and sulfonamide (-S(=O)<sub>2</sub>NH<sub>2</sub>, -S(=O)<sub>2</sub>NHR<sup>21</sup>, or -S(=O)<sub>2</sub>NR<sup>21</sup>R<sup>22</sup>), where R<sup>20</sup>, R<sup>21</sup>, and R<sup>22</sup> are independently selected from a C<sub>1</sub>-C<sub>6</sub> alkyl group; and wherein the electron withdrawing group is selected from halo, cyano (-CN), haloalkyl, carboxamide, nitro, aldehyde (-CHO), keto (-COR<sup>20</sup>), alkenyl, alkynyl, quaternary amino (-N<sup>+</sup>R<sup>20</sup>R<sup>21</sup>R<sup>22</sup>), ester (-COOR<sup>20</sup>), amide (-CONH<sub>2</sub>), mono-substituted amide (-CONHR<sup>20</sup>), disubstituted amide (-CONR<sup>21</sup>R<sup>22</sup>), N-connected amide (-NH<sub>2</sub>-C(=O)-R<sup>20</sup>), mono-substituted N-connected amide (-NHR<sup>21</sup>-C(=O)-R<sup>20</sup>), disubstituted N-connected amide (-NR<sup>21</sup>R<sup>22</sup>-S(=O)<sub>2</sub>-R<sup>20</sup>), N-connected sulfonamide (-NH<sub>2</sub>-S(=O)<sub>2</sub>-R<sup>20</sup>), mono-substituted N-connected sulfonamide (-NHR<sup>21</sup>-S(=O)<sub>2</sub>-R<sup>20</sup>), disubstituted N-connected sulfonamide (-NR<sup>21</sup>R<sup>22</sup>-S(=O)<sub>2</sub>-R<sup>20</sup>), sulphonyl (-S(=O)<sub>2</sub>OH), sulphonate (S(=O)<sub>2</sub>OR<sup>20</sup>), sulphonyl (S(=O)<sub>2</sub>R<sup>20</sup>), and sulfonamide (-S(=O)<sub>2</sub>NH<sub>2</sub>, -S(=O)<sub>2</sub>NHR<sup>21</sup>, or -S(=O)<sub>2</sub>NR<sup>21</sup>R<sup>22</sup>), where R<sup>20</sup>, R<sup>21</sup>, and R<sup>22</sup> are independently a C<sub>1</sub>-C<sub>6</sub> alkyl group.

18. (Withdrawn) The protected anti-neoplastic agent of claim 1, wherein the anti-neoplastic agent is bonded to the hypoxic activator (Hyp) or linking group (L) through an -O- or -NR<sub>5</sub>- group in the anti-neoplastic agent, where R<sub>5</sub> is -H, or C<sub>1</sub>-C<sub>6</sub> alkyl, optionally substituted with one or more groups selected from hydroxyl, ether, thiol, thioether, sulfinic ester, sulfoxide, sulfone, sulfonic acid, sulfonic acid ester, sulfenamide, sulfonamide, carboxylic acid, carboxylic acid salt, ester, amide, aldehyde, keto, amino, halo, and cyano.

19. (Withdrawn) The protected anti-neoplastic agent of claim 1, wherein the anti-neoplastic agent is selected from the group consisting of doxorubicin, daunorubicin, duocarmycin, etoposide, duetoposide, Combretastatin A-4, vinblastine, vincristine,

camptothecin, topotecan, 5-fluorouracil, AQ4N, hydroxyurea, maytansines, enediyenes, discodermolides, epothilones, taxanes, calicheamicins, tedanolides, bleomycins, calicheamicins, colchicine, cytarabine, dacarbazine, dactinomycin, discodermolides, epirubicin, epirubicin derivatives, fludarabine, hydroxyureapentostatin, 6-mercaptopurine, methotrexate, mitomycin, mitoxantrone, carboplatin, cisplatin, prednisone, procarbazine, taxanes, docetaxel, paclitaxel, tedanolides, teniposide, 6-thioguanine, vinca alkaloids, cyclophosphamides, platinum coordination complexes, anthracenediones, substituted ureas, and methylhydrazine derivatives.

20. (Canceled)

21. (Withdrawn) The protected anti-neoplastic agent of claim 1, wherein the compound released upon reduction of the hypoxic activator has an  $IC_{50}$  of less than about 100nM.

22. (Withdrawn) The protected anti-neoplastic agent of claim 1, wherein the anti-neoplastic agent is bonded to the hypoxic activator (Hyp) or linking group (L) by an -O- group in the anti-neoplastic agent, and wherein the -O- group is bonded to an aromatic group in the anti-neoplastic agent.

23. (Canceled)

24. (Withdrawn) The protected anti-neoplastic agent of claim 1, wherein  $R_6$  is unsubstituted  $C_1-C_{10}$  alkyl or  $C_1-C_{10}$  alkyl substituted with one or more heteroatom containing groups selected from hydroxyl, ether, thiol, thioether, sulfinic ester, sulfoxide, sulfone, sulfonic acid, sulfonic acid ester, sulfenamide, sulfonamide, carboxylic acid, carboxylic acid salt, ester, amide, aldehyde, keto, amino, halo, and cyano; and

$R_7$  is hydrogen, unsubstituted  $C_1-C_{10}$  alkyl, or  $C_1-C_{10}$  alkyl substituted with one or more heteroatom containing groups selected from hydroxyl, ether, thiol, thioether, sulfinic ester, sulfoxide, sulfone, sulfonic acid, sulfonic acid ester, sulfenamide, sulfonamide, carboxylic acid, carboxylic acid salt, ester, amide, aldehyde, keto, amino, halo, and cyano.

25. (Canceled)

26. (Withdrawn) The protected anti-neoplastic agent of claim 1, wherein  $R_6$  is unsubstituted  $C_1$ - $C_{10}$  alkyl; and  $R_7$  is hydrogen or unsubstituted  $C_1$ - $C_{10}$  alkyl.

27-28. (Canceled)

29. (Withdrawn) The protected anti-neoplastic agent of claim 1, wherein the spacer group Y is an unsubstituted  $-(CH_2)_n-$  chain with  $n=1-4$ , or a  $-(CH_2)_n-$  chain with  $n=1-4$  substituted with one or more heteroatom containing groups selected from hydroxyl, ether, thiol, thioether, sulfinic ester, sulfoxide, sulfone, sulfonic acid, sulfonic acid ester, sulfenamide, sulfonamide, carboxylic acid, carboxylic acid salt, ester, amide, aldehyde, keto, amino, halo, and cyano.

30-38. (Canceled)

39. (Withdrawn) The protected anti-neoplastic agent of claim 1, wherein X is the acetal group and Y is  $-(CR^eR^f)-R^m-(CR^jR^k)-(CH_2)-$ , where  $R^e$ ,  $R^f$  are independently hydrogen, unsubstituted  $C_1$ - $C_3$  alkyl,  $C_1$ - $C_3$  alkyl substituted with one or more of hydroxyl, ether, thiol, thioether, sulfinic ester, sulfoxide, sulfone, sulfonic acid, sulfonic acid ester, sulfenamide, sulfonamide, carboxylic acid, carboxylic acid salt, ester, amide, aldehyde, keto, amino, halo, and cyano, or  $(CR^eR^f)$  is  $(C=O)$ ;  $R^j$  and  $R^k$  are independently hydrogen, unsubstituted  $C_1$ - $C_3$  alkyl,  $C_1$ - $C_3$  alkyl substituted with one or more of hydroxyl, ether, thiol, thioether, sulfinic ester, sulfoxide, sulfone, sulfonic acid, sulfonic acid ester, sulfenamide, sulfonamide, carboxylic acid, carboxylic acid salt, ester, amide, aldehyde, keto, amino, halo, and cyano, or  $(CR^jR^k)$  is  $(C=O)$ ; and  $R^m$  is selected from  $-O-$ ,  $-S-$ ,  $-S(=O)_2-$ , and  $-NR^{30}-$ , where  $R^{30}$  is selected from  $-C(=O)R^{31}$ ,  $-C(=O)NR^{31}R^{32}$ ,  $-H$ ,  $C_1$ - $C_{10}$  alkyl or  $C_1$ - $C_{10}$  alkyl substituted with one or more heteroatom containing groups selected from hydroxyl, ether, thiol, thioether, sulfinic ester, sulfoxide, sulfone, sulfonic acid, sulfonic acid ester, sulfenamide, sulfonamide, carboxylic acid, carboxylic acid salt, ester, amide, aldehyde, keto, amino, halo, and cyano; and  $R^{31}$  and  $R^{32}$  are independently selected from  $C_1$ - $C_{10}$  alkyl or  $C_1$ - $C_{10}$  alkyl substituted with one or more

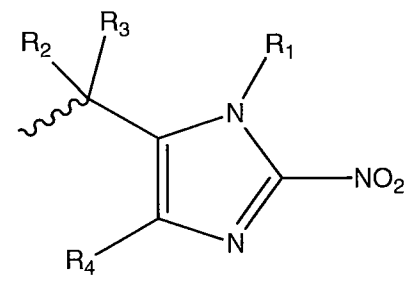
heteroatom containing groups, selected from hydroxyl, ether, thiol, thioether, sulfinic ester, sulfoxide, sulfone, sulfonic acid, sulfonic acid ester, sulfenamide, sulfonamide, carboxylic acid, carboxylic acid salt, ester, amide, aldehydo, keto, amino, halo, and cyano.

40. (Canceled)

41. (Withdrawn) The protected anti-neoplastic agent of claim 1, wherein Y is the delayed release group and has the formula  $\sim R_{10}-R_{11}-R_{12}\sim$  where  $R_{10}$  is a bond;  $R_{11}$  is an unsubstituted or substituted aryl or heteroaryl group; and  $R_{12}$  has the formula  $-(CR^{40}R^{41})-R^{42}-$  or  $-(CR^{40}R^{41})-CR^{43}=CR^{44}-R^{42}-$ , where  $R^{42}$  is a bond or  $-OC(=O)-$ , and  $R^{40}$ ,  $R^{41}$ ,  $R^{42}$ , and  $R^{43}$  are independently selected from  $-H$ , unsubstituted  $C_1-C_{10}$  alkyl, and  $C_1-C_{10}$  alkyl substituted with one or more heteroatom containing groups selected from hydroxyl, ether, thiol, thioether, sulfinic ester, sulfoxide, sulfone, sulfonic acid, sulfonic acid ester, sulfenamide, sulfonamide, carboxylic acid, carboxylic acid salt, ester, amide, aldehydo, keto, amino, halo, and cyano.

42-52. (Canceled)

53. (Currently Amended) A protected anti-neoplastic agent, in which the anti-neoplastic agent is an alkylating agent, and includes one or more protectable hydroxyl groups or amine groups, and wherein one or more of the protectable hydroxyl groups or amine groups is substituted with a group selected from Hyp-L- or Hyp-, wherein Hyp is a hypoxic activator having the formula



wherein  $R_1$  is substituted or unsubstituted  $C_1-C_6$  alkyl or substituted or unsubstituted  $C_1-C_6$  alkoxy;

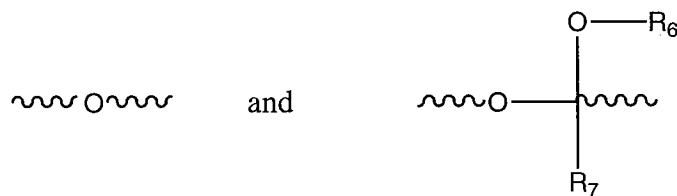
R<sub>2</sub> is hydrogen;

R<sub>3</sub> is -H or C<sub>1</sub>-C<sub>6</sub> alkyl; and

R<sub>4</sub> is -H, substituted or unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl, or substituted or unsubstituted C<sub>1</sub>-C<sub>6</sub> alkoxy;

wherein the R<sub>1</sub> and R<sub>4</sub> substituted alkyl and substituted alkoxy are independently substituted with one or more heteroatom-containing groups selected from ether (-OR<sup>20</sup>), amino (-NH<sub>2</sub>), mono-substituted amino (-NR<sup>20</sup>H), di-substituted amino (-NR<sup>21</sup>R<sup>22</sup>), cyclic C<sub>1-5</sub> alkylamino, imidazolyl, C<sub>1-6</sub> alkylpiperazinyl, morpholino, thiol (-SH), thioether -(SR<sup>20</sup>), tetrazole, carboxylic acid (-COOH), ester (-COOR<sup>20</sup>), amide (-CONH<sub>2</sub>), mono-substituted amide (-CONHR<sup>20</sup>), disubstituted amide (-CONR<sup>21</sup>R<sup>22</sup>), N-connected amide (-NH<sub>2</sub>-C(=O)-R<sup>20</sup>), mono-substituted N-connected amide (-NHR<sup>21</sup>-C(=O)-R<sup>20</sup>), disubstituted N-connected amide (-NR<sup>21</sup>R<sup>22</sup>-S(=O)<sub>2</sub>-R<sup>20</sup>), N-connected sulfonamide (-NH<sub>2</sub>-S(=O)<sub>2</sub>-R<sup>20</sup>), mono-substituted N-connected sulfonamide (-NHR<sup>21</sup>-S(=O)<sub>2</sub>-R<sup>20</sup>), disubstituted N-connected sulfonamide (-NR<sup>21</sup>R<sup>22</sup>-S(=O)<sub>2</sub>-R<sup>20</sup>), sulphonyl (S(=O)<sub>2</sub>R<sup>20</sup>), sulphoxy (S(=O)<sub>2</sub>OH), sulphonate (S(=O)<sub>2</sub>OR<sup>20</sup>), sulphixy (S(=O)OH), sulphinate (S(=O)OR<sup>20</sup>), sulphinyl (S(=O)R<sup>20</sup>), phosphonooxy (OP(=O)(OH)<sub>2</sub>), phosphate (OP(=O)(OR<sup>20</sup>)<sub>2</sub>), and sulfonamide (-S(=O)<sub>2</sub>NH<sub>2</sub>, -S(=O)<sub>2</sub>NHR<sup>21</sup>, or -S(=O)<sub>2</sub>NR<sup>21</sup>R<sup>22</sup>), where R<sup>20</sup>, R<sup>21</sup>, and R<sup>22</sup> are independently selected from a C<sub>1</sub>-C<sub>6</sub> alkyl group; and

L is a linking group of the formula  $\sim\sim\sim X - Y \sim\sim\sim$ , where X is selected from



~~where~~wherein R<sub>6</sub> is unsubstituted alkyl or alkyl substituted with one or more heteroatom containing groups;

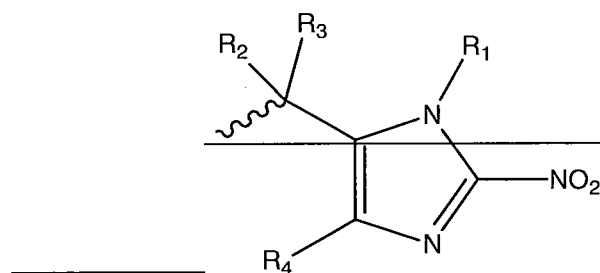
R<sub>7</sub> is hydrogen, unsubstituted alkyl or alkyl substituted with one or more heteroatom containing groups; and



Y is a spacer group selected from a substituted or unsubstituted  $-(CH_2)_n-$  chain with  $n=1-4$ ; a substituted or unsubstituted  $-(CH_2)_n-$  chain with  $n=1-4$  in which one of the carbon backbone chain atoms is substituted by a heteroatom containing group; or a delayed release group comprising an aromatic group.

54. (Canceled)

55. (Currently Amended) The protected anti-neoplastic agent of claim 53[[54]], wherein ~~the hypoxic activator is a nitroimidazole of the formula~~



wherein

——  $R_2$  is hydrogen;

——  $R_3$  is H or  $C_1-C_6$  alkyl;

——  $R_1$  is substituted or unsubstituted  $C_1-C_6$  alkyl or substituted or unsubstituted  $C_1-C_6$  alkoxy; and

——  $R_4$  is H, substituted or unsubstituted  $C_1-C_6$  alkyl, or substituted or unsubstituted  $C_1-C_6$  alkoxy;

—— wherein the  $R_1$  and  $R_4$  substituted alkyl and substituted alkoxy are independently substituted with one or more heteroatom containing groups selected from ether ( $OR^{20}$ ), amino ( $NH_2$ ), mono-substituted amino ( $NR^{20}H$ ), di-substituted amino ( $NR^{21}R^{22}$ ), cyclic  $C_{1-5}$  alkylamino, imidazolyl,  $C_{1-6}$  alkylpiperazinyl, morpholino, thiol ( $SH$ ), thioether ( $SR^{20}$ ), tetrazole, carboxylic acid ( $COOH$ ), ester ( $COOR^{20}$ ), amide ( $CONH_2$ ), mono-substituted amide ( $CONHR^{20}$ ), disubstituted amide ( $CONR^{21}R^{22}$ ), N-connected amide ( $NH_2-C(=O)-R^{20}$ ), mono-substituted N-connected amide ( $NHR^{21}-C(=O)-R^{20}$ ), disubstituted N-connected amide ( $NR^{21}R^{22}-S(=O)_2-R^{20}$ ), N-connected sulfonamide ( $NH_2-S(=O)_2-R^{20}$ ), mono-substituted N-

~~connected sulfonamide ( $\text{NHR}^{21}\text{-S(=O)}_2\text{-R}^{20}$ ), disubstituted N-connected sulfonamide ( $\text{NR}^{21}\text{R}^{22}\text{-S(=O)}_2\text{-R}^{20}$ ), sulphonyl ( $\text{S(=O)}_2\text{OH}$ ), sulphonate ( $\text{S(=O)}_2\text{OR}^{20}$ ), sulphonyl ( $\text{S(=O)}_2\text{R}^{20}$ ), sulphoxy ( $\text{S(=O)OH}$ ), sulphinate ( $\text{S(=O)OR}^{20}$ ), sulphinyl ( $\text{S(=O)R}^{20}$ ), phosphonoxy ( $\text{OP(=O)(OH)}_2$ ), phosphate ( $\text{OP(=O)(OR}^{20})_2$ ), and sulfonamide ( $\text{S(=O)}_2\text{NH}_2$ ,  $\text{S(=O)}_2\text{NHR}^{21}$ , or  $\text{S(=O)}_2\text{NR}^{21}\text{R}^{22}$ ), where  $\text{R}^{20}$ ,  $\text{R}^{21}$ , and  $\text{R}^{22}$  are independently selected from a  $\text{C}_1\text{-C}_6$  alkyl group; and~~

~~L is a linking group of the formula  $\text{---X---Y---}$ , where X is selected from~~

~~R6 is unsubstituted C1-C3 alkyl or C1-C3 alkyl substituted with one or more heteroatom containing groups selected from hydroxyl, ether, thiol, thioether, sulfinic ester, sulfoxide, sulfone, sulfonic acid, sulfonic acid ester, sulfenamide, sulfonamide, carboxylic acid, carboxylic acid salt, ester, amide, aldehyde, keto, amino, halo, and cyano;~~

~~R7 is hydrogen, unsubstituted C1-C3 alkyl, or C1-C3 alkyl substituted with one or more heteroatom containing groups selected from hydroxyl, ether, thiol, thioether, sulfinic ester, sulfoxide, sulfone, sulfonic acid, sulfonic acid ester, sulfenamide, sulfonamide, carboxylic acid, carboxylic acid salt, ester, amide, aldehyde, keto, amino, halo, and cyano; and~~

~~the spacer group Y is an unsubstituted  $\text{-(CH}_2\text{)}_n\text{-}$  chain with  $n=1\text{-}4$ , or a  $\text{-(CH}_2\text{)}_n\text{-}$  chain with  $n=1\text{-}4$  substituted with one or more heteroatom containing groups selected from hydroxyl, ether, thiol, thioether, sulfinic ester, sulfoxide, sulfone, sulfonic acid, sulfonic acid ester, sulfenamide, sulfonamide, carboxylic acid, carboxylic acid salt, ester, amide, aldehyde, keto, amino, halo, and cyano; or~~

~~the spacer group Y is the delayed release group and has the formula~~

~~$\text{---R}_{10}\text{---R}_{11}\text{---R}_{12}\text{---}$  where R10 is a bond; R11 is an unsubstituted or substituted aryl or substituted or unsubstituted heteroaryl group; and R12 has the formula  $\text{-(CR}^{40}\text{R}^{41})\text{-R}^{42}\text{-}$  or  $\text{(CR}^{40}\text{R}^{41})\text{-CR}^{43}\text{=CR}^{44}\text{-R}^{42}\text{-}$ , where  $\text{R}^{42}$  is a bond or  $\text{-OC(=O)-}$ , and  $\text{R}^{40}$ ,  $\text{R}^{41}$ ,  $\text{R}^{42}$ , and  $\text{R}^{43}$  are independently selected from  $\text{-H}$ , unsubstituted  $\text{C}_1\text{-C}_{10}$  alkyl, and  $\text{C}_1\text{-C}_{10}$  alkyl substituted with one or more heteroatom containing groups selected from hydroxyl, ether, thiol, thioether, sulfinic ester, sulfoxide, sulfone, sulfonic acid, sulfonic acid ester, sulfenamide, sulfonamide, carboxylic acid, carboxylic acid salt, ester, amide, aldehyde, keto, amino, halo, and cyano.}~~

56-63. (Canceled)

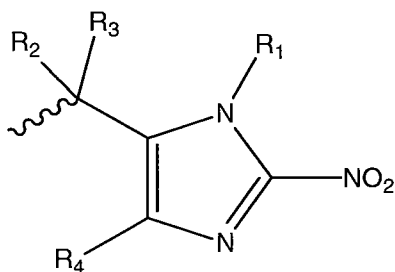
64. (Withdrawn) A method for treating cancer comprising administering to a subject a therapeutically effective amount of a protected anti-neoplastic agent according to claim 1.

65-87. (Canceled)

88. (Currently Amended) A method for treating cancer comprising administering to a subject a therapeutically effective amount of a protected anti-neoplastic agent according to claim 53, wherein the cancer is selected from the group consisting of colon cancer, prostate cancer, lung cancer, non-small cell lung cancer, liver cancer, skin cancer, sarcomas, pancreatic cancer, breast cancer, head and neck cancer, and myeloma.

89. (Currently Amended) A protected anti-neoplastic agent of formula Hyp-L-N or Hyp-N,

wherein Hyp is a hypoxic activator moiety of formula



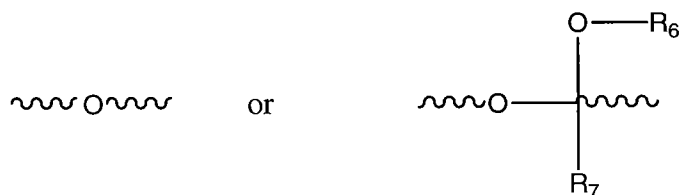
wherein R<sub>1</sub> is unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkyl substituted with one or more heteroatom-containing groups, unsubstituted C<sub>1</sub>-C<sub>6</sub> alkoxy, or C<sub>1</sub>-C<sub>6</sub> alkoxy substituted with one or more heteroatom-containing groups;

R<sub>2</sub> is hydrogen;

R<sub>3</sub> is hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl; and

R<sub>4</sub> is hydrogen, unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkyl substituted with one or more heteroatom-containing groups, unsubstituted C<sub>1</sub>-C<sub>6</sub> alkoxy, or C<sub>1</sub>-C<sub>6</sub> alkoxy substituted with one or more heteroatom-containing groups;

L is a linking group of the formula  $\sim\sim\sim X-Y \sim\sim\sim$ , wherein X is selected from



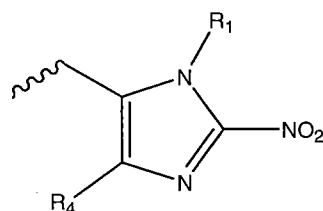
wherein  $R_6$  is unsubstituted alkyl or alkyl substituted with one or more heteroatom containing groups;

$R_7$  is hydrogen, unsubstituted alkyl or alkyl substituted with one or more heteroatom containing groups; and

Y is a spacer group selected from a substituted or unsubstituted  $-(CH_2)_n-$  chain with  $n=1-4$ ; a substituted or unsubstituted  $-(CH_2)_p-HAC-(CH_2)_q-$  chain wherein each p and q independently is 1 – 3 and  $p + q$  is less than or equal to 3 and HAC is a heteroatom containing group; and a delayed release group comprising an aromatic group; and

N is an anti-neoplastic alkylating agent selected from the group consisting of ~~adrenocortical suppressants, alkylating agents, anthracyclines, antibiotics, antimetabolites, aromatase inhibitors, bisphosphonates, cyclo-oxygenase inhibitors, estrogen receptor modulators, folate antagonists, inorganic arsenates, methylhydrazine derivatives, microtubule polymerization perturbors, modifiers, nitrosoureas, nucleoside analogs, osteoclast inhibitors, platinum containing compounds, retinoids, substituted ureas, topoisomerase 1 inhibitors, topoisomerase 2 inhibitors, and tyrosine kinase inhibitors.~~

90. (Currently Amended) The protected anti-neoplastic agent of claim 89 wherein Hyp is of the formula



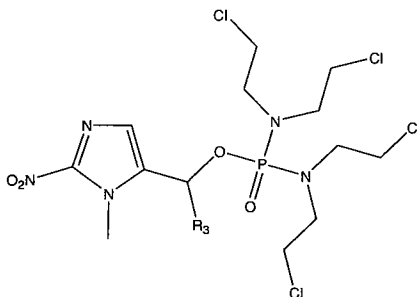
wherein  $R_1$  and  $R_4$  are each independently hydrogen or alkyl selected from methyl, ethyl, n-propyl, n-butyl, n-pentyl, t-butyl, cyclohexyl, cyclopentyl, and isopropyl, wherein the alkyl is

optionally substituted with one or more heteroatom-containing groups; with the proviso that R<sub>1</sub> is not hydrogen.

91. (Canceled)

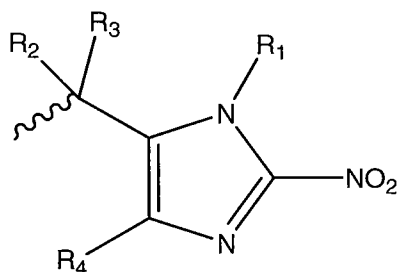
92. (Currently Amended) The protected anti-neoplastic agent of claim 90[[91]] wherein the alkylating agent is selected from the group consisting of cyclophosphamide, ifosfamide, melphalan, chlorambucil, thiotepa, and analogs thereof.

93. (Previously Presented) The protected anti-neoplastic agent of claim 89 of formula



wherein R<sub>3</sub> is hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl.

94. (Withdrawn) A protected anti-neoplastic agent of formula Hyp-L-N, wherein N is an anti-neoplastic agent;  
Hyp is a hypoxic activator moiety of formula



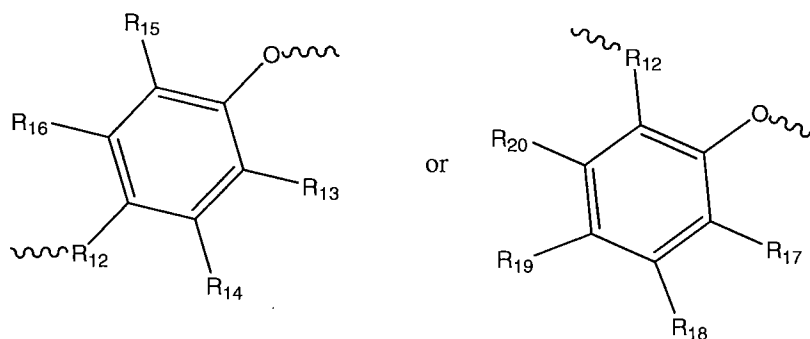
wherein R<sub>2</sub> is hydrogen;

R<sub>3</sub> is hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl; and

R<sub>1</sub> and R<sub>4</sub> are each independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl or C<sub>1</sub>-C<sub>6</sub> alkoxy, the alkyl or alkoxy being optionally substituted with one or more groups selected from ether (-

OR<sup>20</sup>), amino (-NH<sub>2</sub>), mono-substituted amino (-NR<sup>20</sup>H), di-substituted amino (-NR<sup>21</sup>R<sup>22</sup>), cyclic C<sub>1-5</sub> alkylamino, imidazolyl, C<sub>1-6</sub> alkylpiperazinyl, morpholino, thiol (-SH), thioether -(SR<sup>20</sup>), tetrazole, carboxylic acid (-COOH), ester (-COOR<sup>20</sup>), amide (-CONH<sub>2</sub>), mono-substituted amide (-CONHR<sup>20</sup>), disubstituted amide (-CONR<sup>21</sup>R<sup>22</sup>), N-connected amide (-NH<sub>2</sub>-C(=O)-R<sup>20</sup>), mono-substituted N-connected amide (-NHR<sup>21</sup>-C(=O)-R<sup>20</sup>), disubstituted N-connected amide (-NR<sup>21</sup>R<sup>22</sup>-S(=O)<sub>2</sub>-R<sup>20</sup>), N-connected sulfonamide (-NH<sub>2</sub>-S(=O)<sub>2</sub>-R<sup>20</sup>), mono-substituted N-connected sulfonamide (-NHR<sup>21</sup>-S(=O)<sub>2</sub>-R<sup>20</sup>), disubstituted N-connected sulfonamide (-NR<sup>21</sup>R<sup>22</sup>-S(=O)<sub>2</sub>-R<sup>20</sup>), sulphoxy (-S(=O)<sub>2</sub>OH), sulphonate (S(=O)<sub>2</sub>OR<sup>20</sup>), sulphonyl (S(=O)<sub>2</sub>R<sup>20</sup>), sulphixy (S(=O)OH), sulphinate (S(=O)OR<sup>20</sup>), sulphinyl (S(=O)R<sup>20</sup>), phosphonooxy (OP(=O)(OH)<sub>2</sub>), phosphate (OP(=O)(OR<sup>20</sup>)<sub>2</sub>), and sulfonamide (-S(=O)<sub>2</sub>NH<sub>2</sub>, -S(=O)<sub>2</sub>NHR<sup>21</sup>, or -S(=O)<sub>2</sub>NR<sup>21</sup>R<sup>22</sup>), wherein R<sup>20</sup>, R<sup>21</sup>, and R<sup>22</sup> are independently selected from a C<sub>1</sub>-C<sub>6</sub> alkyl group, a C<sub>3</sub>-C<sub>20</sub> heterocyclic group, or a C<sub>3</sub>-C<sub>20</sub> aryl group, preferably a C<sub>1</sub>-C<sub>6</sub> alkyl group; and with the proviso that R<sub>1</sub> is not hydrogen;

L is a linking group having the formula



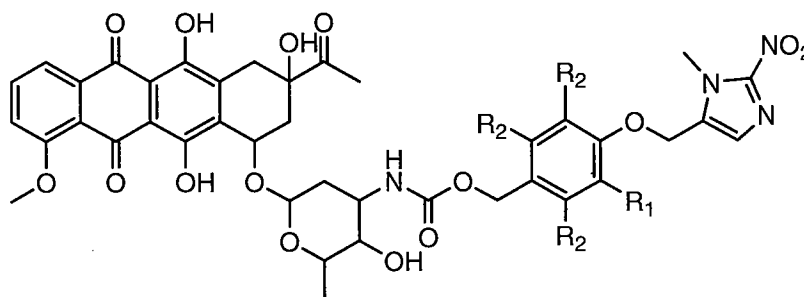
wherein R<sub>12</sub> has the formula -(CR<sup>40</sup>R<sup>41</sup>)-R<sup>42</sup>- or -(CR<sup>40</sup>R<sup>41</sup>)-CR<sup>43</sup>=CR<sup>44</sup>-R<sup>42</sup>-, wherein R<sup>42</sup> is a bond or -OC(=O)-, and R<sup>40</sup>, R<sup>41</sup>, R<sup>42</sup>, and R<sup>43</sup> are independently selected from hydrogen, unsubstituted C<sub>1</sub>-C<sub>10</sub> alkyl, and C<sub>1</sub>-C<sub>10</sub> alkyl substituted with one or more heteroatom containing groups selected from hydroxyl, ether, thiol, thioether, sulfinic ester, sulfoxide, sulfone, sulfonic acid, sulfonic acid ester, sulfenamide, sulfonamide, carboxylic acid, carboxylic acid salt, ester, amide, aldehyde, keto, amino, halo, and cyano; and

each of R<sub>13</sub>-R<sub>19</sub> and R<sub>23</sub> are independently selected from hydrogen, an electron withdrawing group, unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl, substituted C<sub>1</sub>-C<sub>6</sub> alkyl, unsubstituted C<sub>1</sub>-

C<sub>6</sub> alkoxy, and substituted C<sub>1</sub>-C<sub>6</sub> alkoxy; wherein the substituted alkyl or alkoxy are independently substituted with one or more groups selected from ether (-OR<sup>20</sup>), amino (-NH<sub>2</sub>), mono-substituted amino (-NR<sup>20</sup>H), di-substituted amino (-NR<sup>21</sup>R<sup>22</sup>), cyclic C<sub>1-5</sub> alkylamino, imidazolyl, C<sub>1-6</sub> alkylpiperazinyl, morpholino, thiol (-SH), thioether -(SR<sup>20</sup>), tetrazole, carboxylic acid (-COOH), ester (-COOR<sup>20</sup>), amide (-CONH<sub>2</sub>), mono-substituted amide (-CONHR<sup>20</sup>), disubstituted amide (-CONR<sup>21</sup>R<sup>22</sup>), N-connected amide (-NH<sub>2</sub>-C(=O)-R<sup>20</sup>), mono-substituted N-connected amide (-NHR<sup>21</sup>-C(=O)-R<sup>20</sup>), disubstituted N-connected amide (-NR<sup>21</sup>R<sup>22</sup>-S(=O)<sub>2</sub>-R<sup>20</sup>), N-connected sulfonamide (-NH<sub>2</sub>-S(=O)<sub>2</sub>-R<sup>20</sup>), mono-substituted N-connected sulfonamide (-NHR<sup>21</sup>-S(=O)<sub>2</sub>-R<sup>20</sup>), disubstituted N-connected sulfonamide (-NR<sup>21</sup>R<sup>22</sup>-S(=O)<sub>2</sub>-R<sup>20</sup>), sulphonyl (-S(=O)<sub>2</sub>OH), sulphonate (S(=O)<sub>2</sub>OR<sup>20</sup>), sulphonyl (S(=O)<sub>2</sub>R<sup>20</sup>), sulphoxy (S(=O)OH), sulphinate (S(=O)OR<sup>20</sup>), sulphinyl (S(=O)R<sup>20</sup>), phosphonooxy (OP(=O)(OH)<sub>2</sub>), phosphate (OP(=O)(OR<sup>20</sup>)<sub>2</sub>), and sulfonamide (-S(=O)<sub>2</sub>NH<sub>2</sub>, -S(=O)<sub>2</sub>NHR<sup>21</sup>, or -S(=O)<sub>2</sub>NR<sup>21</sup>R<sup>22</sup>), wherein R<sup>20</sup>, R<sup>21</sup>, and R<sup>22</sup> are independently selected from a C<sub>1</sub>-C<sub>6</sub> alkyl group, and

wherein the electron withdrawing group is selected from halo, cyano (-CN), haloalkyl, carboxamide, nitro, aldehydo (-CHO), keto (-COR<sup>20</sup>), alkenyl, alkynyl, quaternary amino (-N<sup>+</sup>R<sup>20</sup>R<sup>21</sup>R<sup>22</sup>), ester (-COOR<sup>20</sup>), amide (-CONH<sub>2</sub>), mono-substituted amide (-CONHR<sup>20</sup>), disubstituted amide (-CONR<sup>21</sup>R<sup>22</sup>), N-connected amide (-NH<sub>2</sub>-C(=O)-R<sup>20</sup>), mono-substituted N-connected amide (-NHR<sup>21</sup>-C(=O)-R<sup>20</sup>), disubstituted N-connected amide (-NR<sup>21</sup>R<sup>22</sup>-S(=O)<sub>2</sub>-R<sup>20</sup>), N-connected sulfonamide (-NH<sub>2</sub>-S(=O)<sub>2</sub>-R<sup>20</sup>), mono-substituted N-connected sulfonamide (-NHR<sup>21</sup>-S(=O)<sub>2</sub>-R<sup>20</sup>), disubstituted N-connected sulfonamide (-NR<sup>21</sup>R<sup>22</sup>-S(=O)<sub>2</sub>-R<sup>20</sup>), sulphonyl (-S(=O)<sub>2</sub>OH), sulphonate (S(=O)<sub>2</sub>OR<sup>20</sup>), sulphonyl (S(=O)<sub>2</sub>R<sup>20</sup>), and sulfonamide (-S(=O)<sub>2</sub>NH<sub>2</sub>, -S(=O)<sub>2</sub>NHR<sup>21</sup>, or -S(=O)<sub>2</sub>NR<sup>21</sup>R<sup>22</sup>), wherein R<sup>20</sup>, R<sup>21</sup>, and R<sup>22</sup> are independently selected from a C<sub>1</sub>-C<sub>6</sub> alkyl group.

95. (Withdrawn) The protected anti-neoplastic agent of claim 94 of formula



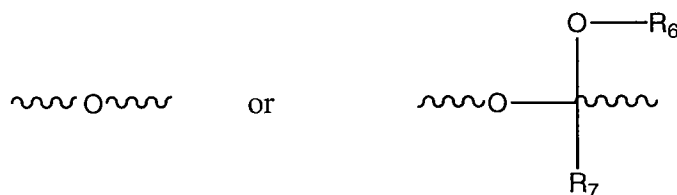
wherein  $R_1$  is selected from nitro and fluoro and  
each  $R_2$  is selected from fluoro and hydrogen.

96. (Withdrawn) A protected anti-neoplastic agent of formula Hyp-L-N or Hyp-N,  
wherein

Hyp is a hypoxic activator moiety;

N is an anti-neoplastic agent;

L is a linking group of the formula  $\sim\sim\sim X-Y \sim\sim\sim$ , wherein X is selected from



wherein  $R_6$  is unsubstituted alkyl or alkyl substituted with one or more  
heteroatom containing groups;

$R_7$  is hydrogen, unsubstituted alkyl or alkyl substituted with one or more  
heteroatom containing groups;

Y is a spacer group selected from a substituted or unsubstituted  $-(CH_2)_n-$  chain with  $n=1-4$ ; a substituted or unsubstituted  $-(CH_2)_p-HAC-(CH_2)_q-$  chain wherein each p and q independently is 1 – 3 and  $p + q$  is less than or equal to 3 and HAC is a heteroatom containing group; and a delayed release group comprising an aromatic group; and

wherein the anti-neoplastic agent (N) is bonded to the hypoxic activator moiety (Hyp) or linking group (L) by an -O- group in the anti-neoplastic agent, and wherein the -O- group is bonded to an aromatic group in the anti-neoplastic agent.

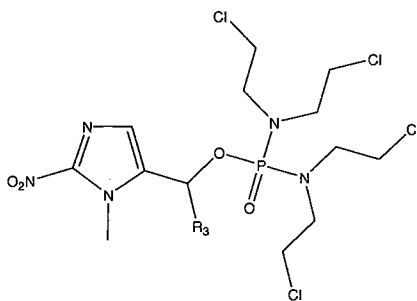


97. (Withdrawn) The protected anti-neoplastic agent of claim 96 wherein the -O- group is bonded to a substituted or unsubstituted phenyl group in the anti-neoplastic agent.

98. (Withdrawn) The protected anti-neoplastic agent of claim 96, wherein the anti-neoplastic agent is selected from the group consisting of barminomycin, combretastatin A-4, daunorubicin, doxorubicin, duocarmycin, etoposide, 10-hydroxycamptothecin, and topotecan.

99. (New) The protected anti-neoplastic agent of claim 55, wherein the alkylating agent is selected from the group consisting of cyclophosphamide, ifosfamide, melphalan, chlorambucil, thiotepa, and analogs thereof.

100. (New) The protected anti-neoplastic agent of claim 99, wherein the alkylating agent is a cyclophosphamide analog and the protected anti-neoplastic agent has the formula



wherein R<sub>3</sub> is hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl.